

## **ETHERS OF O-DESMETHYL VENLAFAXINE**

This is a continuation-in-part of U.S. Serial No. 10/315,699 filed December 10, 2002, which is a divisional of U.S. Serial No. 09/989,000 filed on November 21, 2001, now U.S. Patent No. 6,503,942, which is a divisional of U.S. Serial No. 09/722,193 filed on November 21, 2000, now U.S. Patent No. 6,348,494, which claims priority to U.S. Serial No. 60/240,922 filed November 24, 1999.

### **Field of the Invention**

10        This invention provides O- $\alpha$ -acyloxyalkyl ethers of 4-[2-(Dimethylamino-1-(1-hydroxycyclohexyl)ethyl]phenol, as well as pharmaceutical compositions and uses thereof.

### **Background of the Invention**

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Various patents and literature references describe the biological activities of venlafaxine, and its salts and analogs. Venlafaxine hydrochloride tablets are marketed by Wyeth-Ayerst Laboratories as EFFEXOR.

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The absolute configuration of the (+) enantiomer of venlafaxine was established as S by a single crystal X-ray analysis of the hydrobromide salt and the anomalous dispersion technique (Yardley et al., J. Med. Chem., 1990, 33, 2899).

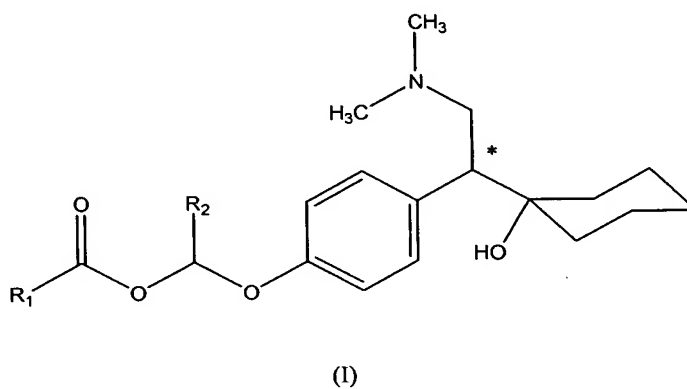
25        (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol and its metabolites 1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol and 1-[1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol are disclosed and claimed in U.S. Patent No. 4,535,186 (Husbands et al.). U.S. Patent No. 5,530,013 (Husbands et al.) claims the use of venlafaxine in the inducement of cognition enhancement. U.S. Patent No. 5,506,270 (Upton et al.) claims venlafaxine's use in methods of  
30        treating hypothalamic amenorrhea in non-depressed women.

U.S. Patents Nos. 5,788,986 (Dodman) and 5,554,383 (Dodman) teaches and claims the use of serotonin reuptake inhibitors in modifying the behavior of dogs.

**Detailed Description of the Invention**

This invention provides pharmaceutically active O- $\alpha$ -acyloxyalkyl ethers of the venlafaxine metabolite 4-[2-(Dimethylamino-1-(1-hydroxycyclohexyl)ethyl] phenol ("O-Desmethyl venlafaxine" or "ODV") having the structural formula I

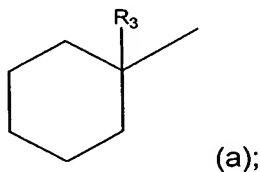
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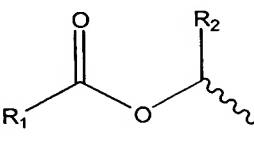
wherein

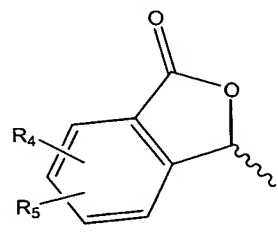
the configuration at the stereogenic center (\*) may be R, S, or RS (the racemate);

10 R<sub>1</sub> is selected from C<sub>1</sub> - C<sub>6</sub> alkyl, C<sub>1</sub> - C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or the moiety:



R<sub>2</sub> is selected from H, or C<sub>1</sub>- C<sub>6</sub> alkyl; or,

R<sub>1</sub> and R<sub>2</sub> may be concatenated such that  , form a

15 moiety having formula (b):  (b);

R<sub>3</sub> is selected from H or C<sub>1</sub> - C<sub>6</sub> alkyl; and

R4 and R5 are independently selected from H, C<sub>1</sub> – C<sub>6</sub> alkyl, C<sub>3</sub>–C<sub>6</sub> cycloalkyl, C<sub>1</sub> – C<sub>6</sub> alkoxy, C<sub>1</sub> – C<sub>6</sub> thioalkoxy, -CN, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, halogen, -NH<sub>2</sub>, -NO<sub>2</sub>, or – N(CH<sub>3</sub>)<sub>2</sub>, or pharmaceutically acceptable salts or hydrates thereof.

In some preferred embodiments of the present invention R1 is t-butyl,  
5 methoxy, or isobenzofuranone.

In other preferred embodiments of the invention R2 is C1-C3 alkyl and in still more preferred embodiments of the invention R2 is methyl.

Specific examples of compounds of Formula I include:

2,2-dimethyl-propionic acid 4-[2-dimethylamino-1-(hydroxy-cyclohexyl)-ethyl]-  
10 phenoxymethylester;

Propionic acid 1-{4-[2-dimethylamino-1-(1-hydroxy-cyclohexyl)-ethyl]-  
phenoxy}-ethyl ester;

[2-[4-(2,2-Dimethyl-propionyloxymethoxy)-phenyl]-2-(1-hydroxy-cyclohexyl)-ethyl]-  
dimethyl-ammonium; 3-carboxy-acrylate; and

15 3-{4-[2-dimethylamino-1-(1-hydroxy-cyclohexyl)-ethyl]-phenoxy}-3*H*-  
isobenzofuran-1-one.

Particularly, this invention provides compounds and/or compositions of both the O- $\alpha$ -acyloxyalkyl R-ether of Formula I and the O- $\alpha$ -acyloxyalkyl S-ether of Formula I, both being substantially free of the other. In addition, the invention  
20 provides the O- $\alpha$ -acyloxyalkyl RS-ether of 4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]-phenol of Formula I.

Substantially free, as used herein means the compound or composition is made up of significantly greater proportion of the desired isomer than of the optical antipode. In a preferred embodiment of the invention, "substantially free" means that  
25 the compound or composition is made up of at least about 90% of the desired isomer and about 10% or less of the optical antipode. In still more preferred embodiments of the present invention, the compound or composition is made up of at least about 95% of the desired isomer and about 5% or less of the optical antipode. In yet further embodiments of the present invention the compound or  
30 composition is made up of at least about 99% of the desired isomer and about 1% or less of the optical antipode. Preferably the characterized or separated enantiomer will exhibit physical properties of a fully characterized compound, i.e. a uniform melting point and a uniform rotation of plane-polarized light in a polarimeter. Most preferably, the enantiomers will be recrystallized to analytical purity.

$C_1 - C_6$  alkyl as used herein, such as in the definition of  $R_1$ , includes straight, branched chain alkyl groups within the specified range of carbon atoms.

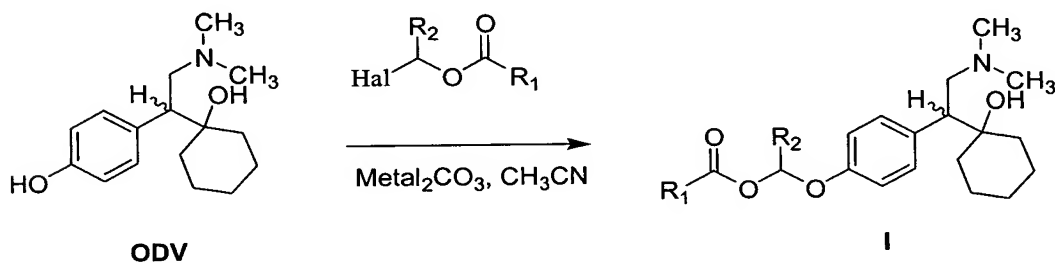
Halogen, as used herein refers to chlorine, bromine, iodine and fluorine.

Pharmaceutically acceptable salts refer to salts prepared from  
 5 pharmaceutically acceptable acids, including inorganic acids and organic acids, such as, but not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic and the like.

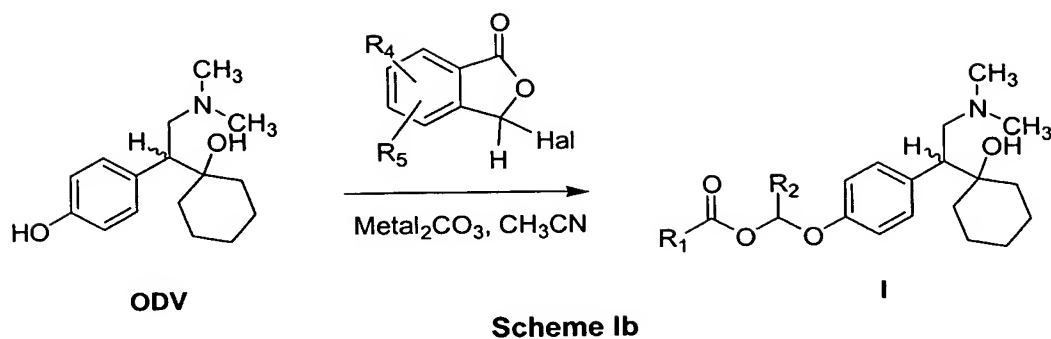
10 Compounds of the invention are readily prepared by methods known in the art, for instance, as described by Bodor, et al., *J. Org. Chem.*(48) 5280-5284 (1983).

The appropriate R-, S-, or (R/S)- 4-[2-(Dimethylamino-1-(1-hydroxycyclohexyl)ethyl]phenol is reacted with the appropriate O- $\alpha$ -acyloxyalkyl halide (examples: pivaloyloxymethyl chloride, 3-bromophthalide, iodomethyl pivalate)  
 15 (Scheme Ia) or (acyloxy)benzyl  $\alpha$ -halide (Scheme Ib) in an inert solvent (acetonitrile, tetrahydrofuran, dimethylformamide) in the presence of an alkali metal carbonate (sodium or potassium carbonate) or transition metal carbonate (silver carbonate) in accordance with Schemes Ia and Ib.

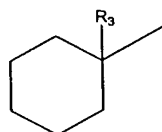
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Scheme Ia



wherein  $R_1$  is selected from  $C_1 - C_6$  alkyl,  $C_1 - C_6$  alkoxy,  $C_3 - C_6$  cycloalkyl, or the moiety:



(a);

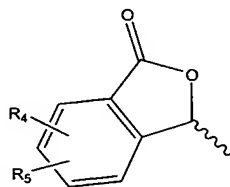
$R_2$  is selected from H, or  $C_1 - C_6$  alkyl,  $C_3 - C_6$  cycloalkyl;

$R_3$  is selected from H or  $C_1 - C_6$  alkyl; and

$R_4$  and  $R_5$  are independently selected from H,  $C_1 - C_6$  alkyl,  $C_3 - C_6$  cycloalkyl,  $C_1 - C_6$  alkoxy,  $C_1 - C_6$  thioalkoxy, -CN, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, halogen, -NH<sub>2</sub>, -NO<sub>2</sub>, or mono or dialkylamino wherein each alkyl group has 1 to 6 carbon atoms.

In some preferred embodiments of the invention increased yield may be obtained by reacting the appropriate R-, S-, or (R/S)- 4-[2-(Dimethylamino-1-(1-hydroxycyclohexyl)ethyl)phenyl]phenol with the appropriate O- $\alpha$ -acyloxyalkyl iodide in an inert solvent (acetonitrile, tetrahydrofuran, dimethylformamide) in the presence of alkali metal carbonate such as potassium carbonate, or transition metal carbonate such as silver carbonate. Most preferred is the use of O- $\alpha$ -acyloxyalkyl iodide in the presence of silver carbonate at low temperatures in the range of approximately 0-5° C.

In a minor modification, compounds of formula I wherein  $R_1$  and  $R_2$  are



concatenated to form , and one or both of  $R_4$  and  $R_5$  are NH<sub>2</sub>, can

be obtained by catalytic reductions, such as with palladium catalysts, from corresponding analogs wherein R<sub>4</sub> or R<sub>5</sub> are NO<sub>2</sub>.

Racemic 1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol can be produced as described in Example 26 of U.S. Patent No. 4,535,186 (Husbands et al.), which is incorporated herein by reference. It will be understood that the enantiomers may be separated from each other by standard resolution techniques known in the art.

Alternatively, these R and S enantiomers may be obtained by O-demethylation of the separated enantiomers of venlafaxine using either boron tribromide or ethane thiol anion.

O- $\alpha$ -acyloxyalkyl ethers of Formula I and their pharmaceutically useful salts and hydrates are useful for the biological and pharmacological activities for which venlafaxine and its salts are known in the art. These O- $\alpha$ -acyloxyalkyl ethers may be used in treating or inhibiting central nervous system disorders, including depression, anxiety, panic disorder, post-traumatic stress disorder, late luteal phase dysphoric disorder (also known as pre-menstrual syndrome), attention deficit disorder, with and without hyperactivity, obsessive compulsive disorder, social phobias, generalized anxiety disorder, bulimia nervosa, Gilles de la Tourette Syndrome, Shy Drager Syndrome, vasomotor flushing, drug and alcohol addiction, sexual dysfunction (including premature ejaculation), borderline personality disorder, chronic fatigue syndrome, fibromyalgia, urinary incontinence, chronic obstructive pulmonary disorder, migraine, Raynaud's syndrome, postherpetic neuralgia, chronic back pain and others. These compounds are also useful in the inducement of cognition enhancement, treatment of obesity and in regimens for cessation of smoking or other tobacco uses.

The compounds of the present invention are further useful for the treatment of senile dementia, Parkinson's Disease, epilepsy, Alzheimer's disease, amnesia, amnesic syndrome, autism, and schizophrenia.

This invention also includes methods of treating, preventing, inhibiting or alleviating each of the maladies listed above in a mammal, preferably in a human, the methods comprising providing a pharmaceutically effective amount of a compound of this invention to the mammal in need thereof.

"Providing" as used herein with respect to providing a compound or substance covered by the invention, means either directly administering such a

compound or substance, or administering a prodrug, derivative or analog which forms an equivalent amount of the compound or substance within the body.

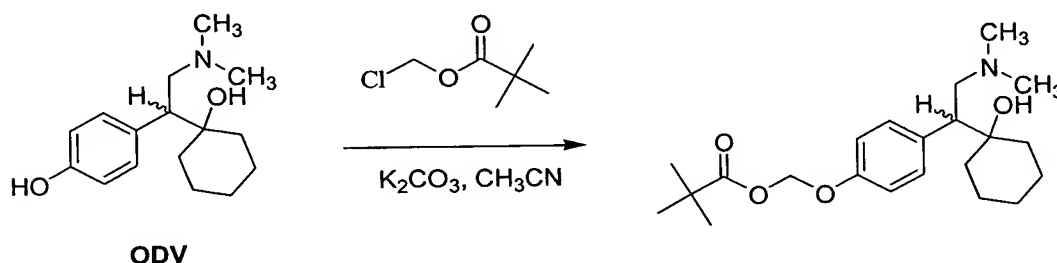
A pharmaceutically effective dose will include those doses which provide the relief or prevention sought for the malady in question. The compounds of this invention may be provided in the dosages and pharmaceutical formulations known in the art as useful for venlafaxine hydrochloride (such as those doses known for the venlafaxine hydrochloride products marketed by Wyeth-Ayerst Laboratories under the Effexor<sup>®</sup> trademark). It will be understood that the initial dose, increases therefrom and final daily administration will be determined by a medical professional considering the needs and conditions for each recipient. For instance, a daily dose for an adult human may be from about 75 mg to about 450 mg per day, preferably between about 75 and about 225 mg per day. An initial dose of 75 mg per day may be administered, with increases as determined by a medical professional.

This invention also includes pharmaceutical compositions comprising a pharmaceutically effective amount of a compound of this invention and one or more pharmaceutically acceptable carriers or excipients. A preferred method of administration includes the use of the present compounds in extended release formulations of the type described in published PCT application WO 99/22724 (Sherman et al.), which is incorporated herein by reference.

The present invention is exemplified, but not limited by, the following specific examples.

#### Example 1

**{4-[2-(Dimethylamino)-1-(1-hydroxy cyclohexyl)ethyl]phenoxy} methyl pivalate.**



4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl) ethyl]phenol (1g, 3.79mmol), chloromethyl pivalate (0.75g, 5mmol), anhydrous  $K_2CO_3$  (0.7 g, 5 mmol) and KI (75mg, 0.5 mmol) were stirred in acetonitrile (50mL) and refluxed overnight. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The ethyl acetate was dried ( $MgSO_4$ ) and evaporated to give the title compound as a minor component.

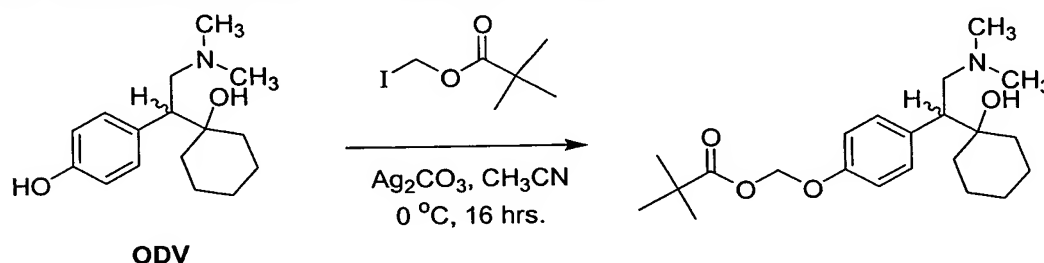
IR (KBr)  $1758cm^{-1}$ .

MS(+)FAB[M+H]<sup>+</sup>378.3 calcd. For  $C_{22}H_{35}NO_4$  377.

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### Example 2

#### {4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}methyl pivalate



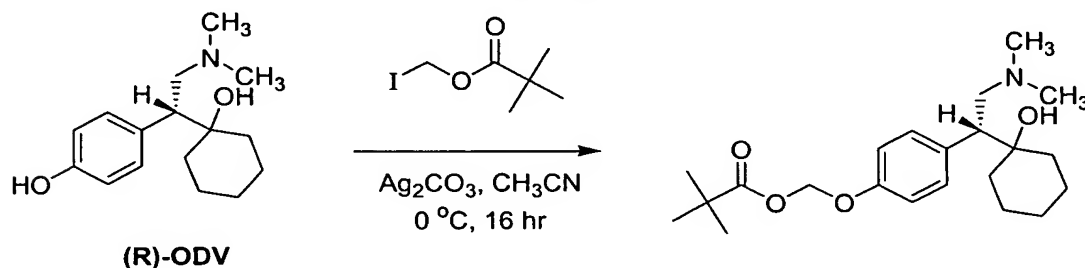
To a solution of ODV (2.0 g, 7.6 mmol) and silver carbonate (8.4 g, 30.4 mmol) in acetonitrile (60 mL) at 0 °C was added a solution of iodomethyl pivalate\* (3.4 g, 14.0 mmol) in acetonitrile (100 mL) dropwise over 4 hr. The reaction mixture was filtered through diatomaceous earth (CELITE, Celite Corporation, Lompoc, CA), then absorbed onto a activated magnesium silicate (60-100 mesh) (FLORISIL, U.S. Silica Company). and purified by column chromatography (FLORISIL, ethyl acetate: acetonitrile 9:1) to afford the title compound (0.87 g, 45 %, based on 68 % conversion) as a yellow tinted semi-solid:  $^1H$  NMR ( $CD_3CN$ )  $\delta$  0.78-1.0 (m, 2H), 1.19 (s, 9H), 1.15-1.35 (m, 4H), 1.4-1.7 (m, 4H), 2.2 (s, 6H), 2.25 (dd,  $J$  = 11.2, 4.5 Hz, 1H), 2.94 (dd,  $J$  = 11.2, 4.5 Hz, 1H), 3.22 (t,  $J$  = 11.2 Hz, 1H), 5.7 (s, 2H), 6.95 (d,  $J$  = 8.7 Hz, 1H), 7.13 (d,  $J$  = 8.7 Hz, 1H);  $^{13}C$ -NMR ( $CD_3CN$ )  $\delta$  22.22, 22.44, 26.91, 27.10 (t), 32.83, 38.78 (t), 39.55 (s), 45.71 (q), 52.58, 61.74, 74.45 (d), 86.78 (t), 116.54, 131.48 (d), 136.68, 156.44, 178.05 (s); MS (EI)  $m/z$  378 ( $M+H$ )<sup>+</sup>; further characterized as the maleate salt. Anal. ( $C_{26}H_{39}NO_8 \cdot 0.25H_2O$ ) Calc: C: 62.69, H: 7.99, N: 2.81, Found: C: 62.68, H: 7.68, N: 2.65.



The celite cake was taken up in brine and extracted with ethyl acetate. Evaporation of the solvent affords 0.65 g (33%) recovered ODV.

### Example 3

#### 5 4-[(1R)-2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenyl pivalate



To a solution of ODV (3.0 g, 11.4 mmol) and silver carbonate (12.6 g, 45.6 mmol) in acetonitrile (300 mL) at 0 °C was added a solution of iodomethyl pivalate\* (6.9 g, 28.5 mmol) in acetonitrile (40 mL) in eight equal portions over 16 hr. The reaction mixture was filtered through diatomaceous earth (CELITE, Celite Corporation, Lompoc, CA), then absorbed onto activated magnesium silicate (60-100 mesh) (FLORISIL, U.S. Silica Company) and purified by column chromatography (FLORISIL, ethyl acetate: acetonitrile 9:1) to afford the title compound (1.15 g, 39 %, based on 60 % conversion) as a white foam: <sup>1</sup>H NMR (CD<sub>3</sub>CN) δ 0.78-1.0 (m, 2H), 1.19 (s, 9H), 1.15-1.35 (m, 4H), 1.4-1.7 (m, 4H), 2.2 (s, 6H), 2.25 (dd, J = 11.2, 4.5 Hz, 1H), 2.94 (dd, J = 11.2, 4.5 Hz, 1H), 3.22 (t, J = 11.2 Hz, 1H), 5.7 (s, 2H), 6.95 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H); <sup>13</sup>C-NMR (CD<sub>3</sub>CN) δ 22.22, 22.44, 26.91, 27.10 (t), 32.83, 38.78 (t), 39.55 (s), 45.71 (q), 52.58, 61.74, 74.45 (d), 86.78 (t), 116.54, 131.48 (d), 136.68, 156.44, 178.05 (s); [α]<sub>D</sub><sup>20</sup> -5.95° (c 1.00, MeOH); MS (EI) m/z 378 (M+H)<sup>+</sup>.

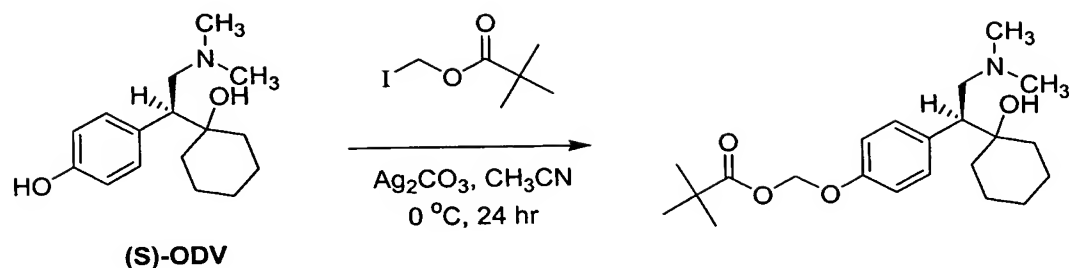
The CELITE cake was taken up in brine and extracted with ethyl acetate.

Evaporation of the solvent affords 1.2 g (40%) recovered ODV.

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### Example 4

#### 4-[(1S)-2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenyl pivalate



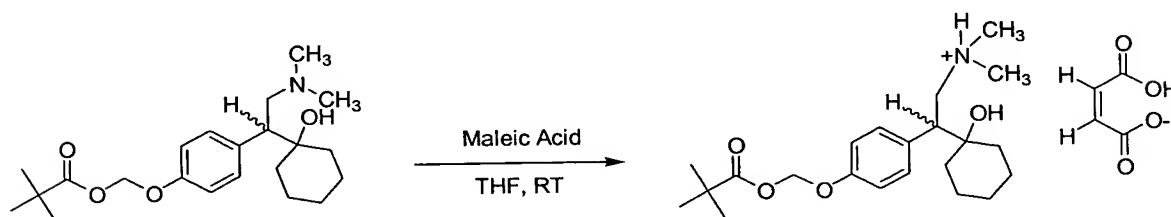
To a solution of ODV (4.0 g, 15.2 mmol) and silver carbonate (16.8 g, 60.8 mmol) in acetonitrile (400 mL) at 0 °C was added a solution of iodomethyl pivalate\* (8.3 g, 34.3 mmol) in acetonitrile (150 mL) over a 9 hr period. The reaction mixture was filtered through diatomaceous earth (CELITE, Celite Corporation, Lompoc, CA), then absorbed onto activated magnesium silicate (60-100 mesh) (FLORISIL, U.S. Silica Company). and purified by column chromatography (FLORISIL, ethyl acetate: acetonitrile 9:1) to afford the title compound (1.58 g, 48 %, based on 57 % conversion) as a clear viscous oil: <sup>1</sup>H NMR (CD<sub>3</sub>CN) δ 0.78-1.0 (m, 2H), 1.19 (s, 9H), 1.15-1.35 (m, 4H), 1.4-1.7 (m, 4H), 2.2 (s, 6H), 2.25 (dd, J = 11.2, 4.5 Hz, 1H), 2.94 (dd, J = 11.2, 4.5 Hz, 1H), 3.22 (t, J = 11.2 Hz, 1H), 5.7 (s, 2H), 6.95 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H); <sup>13</sup>C-NMR (CD<sub>3</sub>CN) δ 22.22, 22.44, 26.91, 27.10 (t), 32.83, 38.78 (t), 39.55 (s), 45.71 (q), 52.58, 61.74, 74.45 (d), 86.78 (t), 116.54, 131.48 (d), 136.68, 156.44, 178.05 (s); [α]<sub>D</sub><sup>20</sup> +7.23° (c 1.00, MeOH); MS (EI) m/z 378 (M+H)<sup>+</sup>.

The CELITE cake was taken up in brine and extracted with ethyl acetate. Evaporation of the solvent affords 1.7 g (43%) recovered ODV.

### Example 5

**{4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}methyl pivalate**

**Maleate salt**



To a solution of {4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}methyl pivalate (0.032 g, 0.085 mmol) prepared as described in Example 1, in THF (1.0 mL) at RT was added a solution of maleic acid (0.007 g, 0.06 mmol) in THF (1.0 mL).  
5 The mixture was warmed and diluted with hexane. The solution was cooled and the resulting crystals filtered off giving the desired maleate salt as a white solid: mp 112-113 °C, <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 0.9-1.6 (m, 10H), 1.13 (s, 9H), 2.7 (br.s, 6H), 2.97 (m, 1H), 3.55 (m, 2H), 4.59 (br.s, 1H), 5.78 (s, 2H), 6.02 (s, 2H), 7.03 (d, *J* = 8.6 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 8.4 (br.s, 1H); MS (EI) *m/z* 378 (M+H)<sup>+</sup>; (C<sub>26</sub>H<sub>39</sub>NO<sub>8</sub>-  
10 0.25H<sub>2</sub>O) Calc: C: 62.69, H: 7.99, N: 2.81, Found: C: 62.68, H: 7.68, N: 2.65.